REMARKS

Reconsideration of the rejections is respectfully requested. By the present amendment, claims 22, 60 and 62 are amended. Thus, claims 22, 23-25, 30, 32, 36, 40, 44-59, 60-65 and 66 are under examination. The number of total claims and of independent claims remains the same.

The claims have been amended to more clearly define the invention. Support for the amendments is apparent from the context.

Summary of the Invention

The present invention relates to polypeptides that trigger cell-mediated immune responses to hepatitis C virus ("HCV"). Cell-mediated immunity provides a mechanism by which abnormal cells, such as virally infected or cancerous cells, are eliminated. This type of immunity is distinct from antibody-mediated immune responses which are typically directed to infectious agents, rather than infected host cells. The molecular basis of cell-mediated immunity has been the object of intensive research, which has yielded a wealth of information.

In a virally infected cell, the viral genome directs the synthesis of viral proteins. In a given time period a portion of these viral proteins, along with normal cell products, are degraded by cellular processes, resulting in fragments that are directed to the cell surface. Appropriate fragments associate with a cell-surface major histocompatibility complex ("MHC"). The MHC with bound fragment is available to be bound by a T-cell receptor ("TCR") found on a cytotoxic T-cell (or cytotoxic T lymphocyte, or "CTL"). T-cell development results in the generation of an associated TCR with one of a large repertoire of binding specificities. Binding by the given TCR can trigger a T-cell response to eliminate the infected cell. Fragments triggering such a response define "cytotoxic T lymphocyte stimulating epitopes." Appropriate polypeptides can be used in conjunction with antigen presenting cells to stimulate *in vitro* expansion of a patient's CTL precursor cells.

Applicants tested 53 candidate cytotoxic T lymphocyte stimulating epitopes derived from HCV, and identified the nine reference sequences (of nine to ten amino acids in length) recited in their claims. Applicants recognized that in addition to these sequences, one of ordinary skill applying the testing taught in the specification, and the facile synthesis or biosynthesis taught in

the specification and known in the art, could make close analogs of the sequences that retain function.

Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

All of the pending claims, claims 22-25, 30, 32, 36, 40 and 44-66, are asserted to be rejected under 35 U.S.C. §112, first paragraph, with the office action dated February 9, 1999 (the "Office Action") asserting that while "disclosure references (see p. 14, lines 14-25) functionally equivalent peptides that can be identified through 'suitable single amino acid substitutions, deletions, or insertions,'" it does not provide support for peptides having no more than two substitutions." The claim recital that is alleged not to be described regards having "no more than a total of two substitutions, deletions or insertions at the corresponding amino acid positions in a CTL epitope." These single amino acid substitutions, deletions or insertions are with respect to any of four reference amino acid sequences:

#	Sequence
1.	LLALLSCLTV ($Core_{178\text{-}187}$; SEQ ID NO:2),
2.	QLRRHIDLLV ($E1_{257\text{-}266}$; SEQ ID NO:3),
3.	KLVALGINAV ($NS3_{1406\text{-}1415}$; SEQ ID NO:28), or
4.	LLFNILGGWV ($NS4_{1807\text{-}1816}$; SEQ ID NO:35).

Applicants are quite confident that the concept at issue is clearly described in the specification. In any case, the concept is at least described with sufficient reasonable clarity to satisfy the patent law.

The description requirement of 35 U.S.C. §112 is imposed to assure that a patent application *reasonably* conveys to one of ordinary skill in the art that the inventors had possession of a claimed invention at the time of the filing date relied upon. Ralson Purina Co. v. Far-Mar Co., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985). To provide this assurance, the specification must reasonably convey to one skilled in the art the subject matter of the claim. A strong theme of the precedent is that the invention need only be reasonably described. A recognized need for flexibility is exemplified in MPEP §2163.02, which states that the claims need not be set forth using the same terms (*in haec verba*) used in the specification. Further confirmation that the rule is flexible, and only intended to guard against an inventor claiming what he or she had not yet invented, is found in case law precedent that sets forth that it

can be sufficient for drawings alone to provide the written description. See, e.g., In re Wolfensperger, 302 F.2d 950, 133 USPQ 537 (CCPA 1962); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111 (Fed.Cir. 1991); Wang Laboratories v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed.Cir. 1993).

For example, one issue in In re Wolfensperger, 302 F.2d 950, 133 USPQ 537 (CCPA 1962) was whether a drawing showing a relative dimension of an O-ring would support a claim limitation reciting that this relative dimension was for the "untensioned" state, even though there was no express description that the illustrated O-ring was in the untensioned state. The Court looked to practical considerations to find the "untensioned" state to be described in this drawing. A further indication of the practical flexibility of the description requirement is that it does not even appear to have been disputed that the drawing *described* the O-ring as having a "mean diameter corresponding approximately to the mean diameter of said chamber."

The practical flexibility of the description requirement extends to allowing the invention to be claimed in words that set forth the concepts found in an application, even though those specific words are not found in the specification. MPEP §2163.02. For instance, in In re Wright, 866 F.2d 422, 9 USPQ2d 1649 (Fed.Cir. 1989), the Court considered whether the phrase "not permanently fixed thereto," which related to photosensitive microcapsules used in a method of forming images, was adequately supported by a specification that did not use these particular words. The court found that the claim limitation was supported. Wright at 425, 9 USPQ2d at 1651. The Court of Customs and Patent Appeals in In re Anderson stated the general rule as follows:

> The question, as we view it, is not whether "carrying" was a word *used* in the specification as filed but whether there is *support* in the specification for employment of the term in a claim; is the concept of carrying present in the original disclosure?

471 F.2d 1237, 1244, 176 USPQ 331, 336 (CCPA 1973)(emphasis in the original).

The specification evidences that the inventors recognized at the time of filing that their invention encompassed the subject matter in question. The original claims were framed in terms of polypeptide segments having *substantial homology* to the reference sequences recited in the claims now at issue. *Substantial homology* is defined as follows:

> Two polypeptides are said to be substantially homologous if at least 50% of the amino acid ("aa") residues are the same in the same or analogous positions.

Specification at 8. Thus, the inventors sought to convey that the invention was broader than to the particular reference sequences recited in the claims. The specification likewise states that the peptides "may be subject to various changes, such as insertions, deletions, and substitutions." Specification at 13. Moreover, "the portion of the sequence that is intended to mimic substantially a HCV cytotoxic T lymphocyte stimulating epitope will not differ by more than about 20% from the sequence of at least one subtype of HCV." Specification at 14. All of the reference sequences at issue are believed to be T lymphocyte stimulating epitopes; and all are ten (10) amino acids in length. Twenty percent of ten amino acids is two amino acids, meaning that the concept conveyed by the specification's language (a total of two substitutions, deletions or insertions) was contemplated to be within the invention. Thus, the assertion that the claim language is unsupported in the specification simply does not withstand scrutiny.

Accordingly, Applicants respectfully submit that the claim concept at issue was described, in accordance with the legal requirements of 35 U.S.C. §112, in the specification as filed.

Moreover, the Office Action acknowledges that the specification supports reciting a single amino acid substitution, deletion or insertion. In view of this latter point, it appears that the claims 30, 32, 36 and 40, which contain recitals in these terms, are erroneously listed under this rejection. Note also that the generic claims recite five additional reference sequences (which we can identify as #'s 5 through 9), but with a recitation of the single amino acid substitution, deletion or insertion language that appears not to be at issue under this rejection.

Rejection Under 35 U.S.C. §112, First Paragraph, Asserted Undue Experimentation

All of the pending claims, claims 22-25, 30, 32, 36, 40 and 44-66, are rejected under 35 U.S.C. §112, first paragraph, with the Office Action asserting that the specification does not reasonably enable a person skilled in the art to which it pertains to make or use an invention commensurate in scope with the claims.

Whether the scope of enablement is sufficient is often decided in light of the following factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance

presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors are illustrative, not mandatory. Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991). A review of these factors as applied to the present claims, supports Applicants' assertion that the claim are enabled, as outlined in subsections (A) through (G) below.

(A) *Quantity Of Experimentation*

The Reece et al. article, which is of record in this application, and which is dated prior to the filing of this application, illustrates that the quantity of experimentation necessary to make and use the present invention was manageable when this application was filed in view of the technology then available. Reece et al., 151 J. IMMUNOL. 6175 (1993). In Reece, in excess of one thousand (1,304) overlapping 12 residue peptide fragments were synthesized by the multipin method to map T-cell epitopes of tetanus toxin. Pools of 20 peptides each were used to simplify the mapping assays. Thus, it was practical to synthesize a large number of peptides, and the initial screen needed only to assay sixty to seventy pools. Pools that generated strong responses were deconvoluted by assaying the members of the pool.

Suppose one focused on Applicants' above-recited polypeptide # 1 of sequence: LeuLeuAlaLeuLeuSerCysLeuThrVal. One could simplify the mapping exercise by maintaining the XLXXXXXXXV or XLXXXXXXV motifs mentioned in the specification. Specification at 44. One could initially seek only one change at a time. Thus, one could design:

Number of Peptides	Modification
8	Deletions
8	Replacement with representative of lys/arg
4	Replacement with representative of leu/ile/val
8	Replacement with representative of asn/gln
8	Replacement with representative of asp/glu
6	Replacement with representative of thr/ser
8	Replacement with gly
7	Replacement with ala

7	Replacement with cys
8	Replacement with representative of phe/tyr
8	Replacement with trp
8	Replacement with his
8	Replacement with met
8	Replacement with pro
104	

Each of the above groupings could comprise a pool. Positive pools would be deconvoluted. Effective polypeptides would be the basis for straightforwardly identifying peptides with two changes. Thus, as illustrated by the mapping of Reece, the quantity of experimentation would be reasonable.

(B) *Amount Of Direction Or Guidance Presented*

The specification is replete with teachings on how to select likely analogs on pages 13-18, including teachings of the above-discussed pooling method to simplify screening. Methods of making the polypeptides chemically or recombinantly are described on pages 21-22. Examples 2-5 illustrate methods of screening the polypeptides. Applicants respectfully submit that this marker of enablement weighs in favor of approving the claims.

(C) *Presence Or Absence Of Working Examples*

The specification abundantly provided with working examples. See, specification at 44-59. Even the roughly 44 less favored polypeptides of Example 1 provide instruction to those attempting to make and use the invention.

(D) *Nature Of The Invention; Predictability Or Unpredictability Of The Art*

The art is no more unpredictable than the chemical arts in general. Thus, the reasonable scope of the claims should be comparable to that which can be achieved with other structure-focused claims in the chemical arts. Moreover, the ease with which the polypeptides are screened, and the availability of robotic automation tools at the time the application was filed, counterbalance this element of the analysis.

(E) *State Of The Prior Art*

Applicants identified the claimed subject matter at a time when a wealth of knowledge on the nature of antigen binding requirements for MHC interaction and recognition by T cells was becoming available. Such knowledge is exemplified by Sette et al., 328 NATURE 395 (1987); Allen et al., 327 NATURE 713 (1987); Rothebard and Gefter, 9 ANN. REV. IMMUNOL. 527 (1991); Falk et al., 351 NATURE 290 (1991). This knowledge would help those of ordinary skill in the art having benefit of Applicants' reference sequences to design variants.

(F) *Relative Skill Of Those In The Art*

In Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1372-74 52 USPQ2d 1129, 1136-38 (Fed. Cir. 1999), the Federal Circuit approved a trial court determination in a comparable art that a person of ordinary skill would be a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience. Applicants respectfully submit that this level of skill is an appropriate measure of skill in the present context.

(G) *Breadth Of The Claims*

The claims focus on structure, including a modest accounting for reasonable variation. The variation is defined concretely in terms of chemical structure. Applicants respectfully submit that the variation encompassed by the "no more than a total of two substitutions, deletions or insertions at the corresponding amino acid positions in a CTL epitope" language at issue is very reasonable, when measured against the ordinary amount of variation allowed in more classical chemical patents.

(H) *Other Issues*

The Office Action has indicated that *in vitro* indicators of CTL epitope are not fully predictive of immunogenicity. This is in essence an assertion of lack of utility. As the discussion below notes, only a reasonable correlation between an activity and an asserted utility is required. See, also, MPEP §2107.02(I). Issues of this type are addressed in more detail in the next section of this Reply. In view of the discussion below, Applicants respectfully submit that this issue should not be probative of the presence or absence of reasonable claim scope.

The bottom line issue, superseding the guidance provided by the above-elucidated optional factors, is whether the invention as claimed can be practiced without undue experimentation. In the attached Declaration Under Rule 132, one of the present inventors, a leading expert in the field, opines with extensive factual support that the invention can be practiced with ordinary experimentation. It is respectfully submitted that this inventor's opinion is due substantial deference, and that moreover the factual support presented by the inventor is dispositive in favor of the Applicants.

In light of the above discussion, Applicants respectfully submit that the rejection asserting that the scope of the claims is too expansive should be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph, Asserted Lack of Utility Nexus

The Office Action asserts that claims 58 and 59 do not satisfy 35 U.S.C. §112, first paragraph, as there is not enough evidence of utility. The prior Utility Examination Guidelines (Sections 2100 *et seq.* of the MPEP) acknowledge that the lack of utility rejection can be framed under 35 U.S.C. §112 or 35 U.S.C. §101, and thus it is clear that the guidance found in the prior Utility Examination Guidelines and the case law on rejections under 35 U.S.C. §101 should inform consideration of this rejection. Under the proposed Revised Utility Examination Guidelines ("Utility Guidelines"), the guidelines are also applicable irrespective of whether the rejection is framed under 35 U.S.C. §112 or 35 U.S.C. §101.

The Office Action asserts that there must be a "reasonable nexus that would the skilled artisan to conclude... that the claimed CTL epitope-containing peptides would produce... [an] ameliorative effect pertaining to the clinical sequelae associated with HCV infection. This nexus is generally provided by performing *in vitro* and *in vivo* testing in a suitable animal model that is reasonably predictive of clinical success." Office Action at 4 (emphasis added). However, as the Federal Circuit emphatically stated in Cross v. Iizuka, 753 F.2d 1040, 1050-1051, 224 USPQ 739, 747-748 (Fed. Cir. 1985), *in vitro* data *reasonably* correlative of *in vivo* activity is sufficient to establish a practical utility. As discussed below, the Utility Examination Guidelines mitigate against the asserted rejection. Applicants further note below that the decisions of the Court of Appeals for the Federal Circuit are even more forceful than the Utility Guidelines in seeking to

limit the scope the Patent Office's inquiry into clinical efficacy where there is sufficient reason to conclude that the claimed invention provides a pharmacological activity.

Under the Utility Guidelines, "Office personnel are reminded *that they must treat as true a statement of fact made by an applicant* in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art *would have a legitimate basis to doubt the credibility of such a statement.*" Utility Guidelines §B.4 (emphasis added). To make a prima facie showing overcoming this presumption, the Office must provide: (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record. Utility Guidelines §B.3(a). This record "must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention." Utility Guidelines §B.3(a).

The language in the Utility Guidelines speaks of a utility that one skilled in the art would not find *credible*. This plain language indicates a high burden on the Office to finding that it is more likely than not that a person skilled in the art would not consider the asserted utility not credible. Any lower burden would render meaningless the presumption in favor of the Applicant's assertion. In fact, in the Office's prior effort to provide guidance on utility, the Office stated that "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art." MPEP 2107.01(III)(A).

In the pharmaceutical arts, *in vitro* test results (where required) need not absolutely prove pharmacological activity. "All that is required is that the tests be '*reasonably*' indicative of the desired [pharmacological] response." Fujikawa v. Wattanasin 93 F.3d 1559, 1564, 39 USPQ2d 1895, 1899 (Fed. Cir. 1996). This case law indicates that "not credible" means more than some reason to question utility, since only a reasonable basis for utility, not absolute proof, is required. "Not credible" means no basis to believe in the utility, or evidence supporting a palpable sense that the invention will not work.

Instead, the Office Action reverses the burden and asks the Applicants to rebut a number of assertions including, as abstracted from the Office Action:[2]

> 1) The art teaches that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule.
>
> 2) The art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation.
>
> 3) The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule.
>
> 4) The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic.
>
> 5) The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities.
>
> 6) The art teaches that natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses.
>
> 7) The art teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients.
>
> (8) The disclosure fails to provide sufficient guidance demonstrating that a vigorous HCV-specific CTL response can be generated in humans, or other mammals, that will result in amelioration of the clinical sequelae associated with HCV infection. As previously set forth, Rehermann *et al.* (1996), observe that patients chronically infected with HCV develop HCV- specific CTL, but these CTL response[s] are unable to clear the infection or produce any immediate salubrious effects. The authors concluded that "these results and the published database suggest that the CTL response probably contributes to disease pathogenesis but is not vigorous enough to eradicate the virus during chronic HCV infection in most patients."
>
> (9) The disclosure fails to identify the correlates of protective immunity as it pertains to HCV infection. Koziel *et al.*(1997), Koff (1993), and Prince (1994) ... note that the correlates of protective immunity remain to be elucidated. Patients, often vigorously, develop HCV-specific CTL responses, but these response are often inadequate and incapable of clearing the virus or providing any substantial ameliorative effects. A number of factors contribute toward this inadequate immune response including the presence of HCV variants that elude immune surveillance, the presence of variant HCV CTL epitopes with altered antigen processing, transport, and presentation properties, and allelic MHC variation within any given patient population. Moreover, Koff (1993) adds that "the general

[2] The abstracted text maintains the sentence structure of the Office Action; citations to the specification are omitted.

> failure to identify a neutralizing, protective humoral immune response in HCV infection coupled with the data described by Farci *et al.* represent an awesome constellation of impediments to the development of a HCV vaccine."
>
> (10) The disclosure fails to provide appropriate *in vitro* systems for the propagation of HCV and assays for the study of infection of cytopathic effects. * * * The art teaches that these systems and assays are not available to the virologist pursuing HCV antivirals (Koff, 1993 and Prince, 1994). As Koff (1993) concludes, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable. Failure to propagate HCV in tissue culture, the absence of simple *in vitro* assays for infection or cytopathic .effects . . . are well known but not insurmountable issues."
>
> (11) The disclosure fails to provide adequate testing of the proposed pharmaceuticals in an art-recognized animal model. Following the preliminary screening of putative antiviral candidates in *in vitro* assays, the skilled artisan generally employs a suitable animal model to further address concerns that are not evident or addressed by *in vitro* screening assays(i.e., pharmacological properties of the putative therapeutic) However, the art teaches that such models are not available to the skilled artisan trying to develop an anti-HCV compound (Koff, 1993). As Koff (1993)reports, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable . .. and the lack of a suitable small-animal model are well known but not insurmountable issues."

Office Action at 6-8. Though Applicants respectfully submit that the burden is not properly placed on them, these assertions are addressed below:

The art teaches that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule: This assertion is a restated rejection for lack of enablement and is properly addressed in the previous section of this Reply.

The prior art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation: This aspect did not appear to have been maintained in the rejection for asserted lack of enablement, but the assertion would be addressed under the standards for enablement. Applicants note that reasonable experimentation would probably initially focus on identifying effective smaller peptides, and then delivery vehicles in larger moieties could reasonably be produced and tested. A prior office action supported this assertion with the following text:

> Eisenlohr et al. (1992) reported that CTL epitopic flanking amino acid residues were critical for the efficient processing and presentation of antigen to CTL. Flanking sequences were capable of either enhancing or abrogating peptide

> processing and recognition. Hahn et al. (1992) disclosed that a single amino acid substitution immediately flanking the recognized CTL epitope significantly curtailed CTL-mediated cell lysis. Additional CTL studies performed by Del Val et al. (1991) documented that "residues that directly flank the antigenic sequence in a protein critically influence the amount of naturally processed and presented antigenic peptide."

Eisenlohr does teach that flanking sequence can be important. But the standard for enablement is whether the invention can be practiced without undue experimentation. Hahn notes that "[m]ost alterations in residues flanking the endogenously expressed epitope do not appreciable affect the generation and recognition of the site [i.e., epitope]." Hahn et al., 176 J. EXP. MED. 1335 (1992). Thus, the Office Action focuses on lessons in Hahn that present exceptions to the general rule taught in Hahn. Applicants respectfully submit that even if some sites are highly restrictive in the amount of substitution, deletion or insertion allowed, the invention can nonetheless be practiced without *undue* experimentation. Del Val teaches one insertion site in a construct for making fusion proteins reduced the activity of a 9-mer *but not the activity of a corresponding 18-mer having native flanking sequence.* Del Val et al., 66 CELL 1145, 1146 (1991). Del Val also provides guidance to the effect that alanine residues at the immediate flanks can ameliorate presentation difficulties such as are found, in one context, for the 9-mer. Del Val at 1147. Thus, Del Val in fact provides guidance for useful avenues to practice the invention to its claimed scope.

The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule: This observation points out why the Applicants screened numerous polypeptides with an MHC class I binding motif prior to selecting the nine that form the basis for the present claims.

The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic: In a prior office action, this assertion is said to be supported by Nayersina et al., 1993; Couillin et al., 1995; and Eisenlohr et al., 1992. "Immunogenic" means that a polypeptide generates a cytotoxic response. The claims at issue recite: "comprising a peptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes." Thus, non-immunogenic peptides are outside the claims. The present

specification teaches testing for such a cytotoxic response, so that the issue again reverts to the enablement issue addressed in the preceding section.

The art teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients): The foundation for this rejection is not clearly set forth in the Office Action, thus Applicants respectfully submit that there is insufficient basis upon which to frame a response. However, it appears likely that the response of the following paragraph is largely applicable here. Moreover, the Offices prior Utility Examination Guidelines expressly and correctly provided that safety considerations are not the Office's domain. MPEP 2107.02(V).

The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities; The art teaches that natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses; The art teaches that patients chronically infected with HCV develop HCV-specific CTL, but these CTL response are unable to clear the infection or produce any immediate salubrious effects: Apparently the implication is that the polypeptides of the invention may not be effective in some patients. First, of course, such speculation does not satisfy the burden on the Office outlined above. Moreover, Applicants respectfully submit that the invention is useful, i.e. provides a benefit to the public, if it benefits some of the recipients.

The art teaches that a number of hurdles remain to be overcome before adoptive immunotherapy will become a reality in the treatment of HCV infection: The art that the Office relies upon appears to again outline why the CTL approach may be difficult to apply in some patients or, in one case, that the CTL approach is at least preferable to the antibody-based approach. Applicants respectfully submit that a practical utility does not imply that a benefit must be achieved in all patients.

The art teaches that appropriate in vitro and in vivo assays and systems are currently not available to the virologist pursuing HCV antivirals; The art teaches that suitable animal modes are not currently available to the skilled artisan trying to develop an anti-HCV compound: Applicants respectfully submit that the final paragraph of MPEP 2107.02(III) correctly made clear that the Office would be asking for far greater proof of efficacy than is appropriate. The

discussion above makes clear that irrespective of any changes in the wording of the Office's internal guidelines, the credible utility requirement of the patent law does not require the exacting proof the Office appears to require here.

The Koff note cited in support of the rejection is a commentary on a report by Farci et al. on experiments with chimpanzees that were, over a course of months, challenged and re-challenged with HCV, where the use of heterologous strains established that the re-challenged chimpanzees were reinfected. Thus, in this model, with a challenge unlike any that the Applicants propose, "protective immunity against reinfection is either absent or weak." Koff, 104 GASTROENTEROLOGY 1228, 1229 (1993). Applicants respectfully submit that the foundation of the Koff commentary is an experiment of little relevance to the Applicants' invention.

The Prince article cited in support of the rejection is a commentary on a report that an HCV vaccine has shown some effectiveness. The commentary is to the effect that such antibody-based vaccines are likely to be difficult to finance, and of less than optimal effectiveness. Because Prince questions the degree of effectiveness of the vaccine (though does not assert complete lack of effectiveness), Prince promotes the use of a CTL approach. Prince, 14 FEMS MICROBIOL. REV. 273, 276 (1994). Applicants respectfully submit that this Prince article does not provide substantial evidence of any lack of utility of their invention.

Applicants respectfully submit that the above discussion points out how the rejection asserting lack of utility does not satisfy the Office's internal guidelines. Moreover, Applicants respectfully submit that the data in their application showing induction of a CTL response in the peripheral mononuclear cells of at least some infected individuals is more than sufficient to demonstrate a pharmaceutical activity. As the Federal Circuit restated in Fujikawa v. Wattanasin:

> In the pharmaceutical arts, our court has long held that practical utility may be shown by adequate evidence of any pharmacological activity. * * * Such activity constitutes a practical utility because "[i]t is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in

> as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility."

93 F.3d 1559, 1564, 39 USPQ2d 1895, 1899 (Fed. Cir. 1996) (citing Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980); In re Krimmel, 292 F.2d 948, 952-53, 130 USPQ 215, 219 (CCPA 1961)).

Applicants respectfully submit that the above-quoted language from the Federal Circuit points out what is required *assuming for the sake of argument* there was sufficient reason to delve into the utility question: sufficient evidence that one of ordinary skill in the art would conclude that more likely than not it would be reasonable to expend resources on the claimed composition. The utility requirement can be met in the pharmaceutical arts even though "it may eventually appear that the compound is without value in the treatment of humans." In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). Structures of the invention stimulate cytotoxic T-cells from HCV-infected individuals to cause cells to lyse peptide-pulsed cells or cells that generated the appropriate peptide presentation by internal processing of HBV-derived protein (Specification at 46-56), and can be used to stimulate *in vitro* production of cytotoxic T-cells of appropriate specificity (Specification at 41). These activities are pharmaceutical activities that provide a practical utility, or real benefit.

In light of the above discussion, Applicants respectfully submit that the rejection under 35 U.S.C. §112, first paragraph, asserting lack of utility, should be withdrawn.

Conclusion

In light of the above discussion and amendments, it is respectfully submitted that the claims are in condition for allowance. The issuance of a Notice of Allowance is earnestly solicited.[3]

Respectfully submitted,

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[3] **FEE DEFICIENCY**

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